ChemComm

Syntheses and thermal reactivities of symmetrically and asymmetrically substituted acyclic enediynes: steric control of Bergman cyclization temperatures

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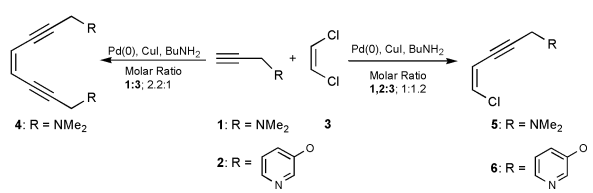
Received (in Corvallis, OR, USA) 6th September 2000, Accepted 6th November 2000
First published as an Advance Article on the web

The steric influences of the functional groups at the termini of acyclic enediynes can dramatically affect the Bergman cyclization temperatures of the resulting compounds.

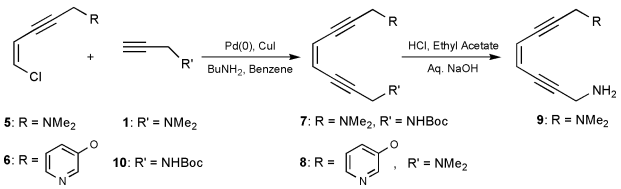
The potent antitumor activity of the enediyne natural product antibiotics[1] such as calicheamicin,[2] dynemicin,[3] esperamicin,[4] and neocarzinostatin[5] has fostered interest in the development of simple enediynes with low thermal barriers to formation of the lethal 1,4-benzenoid diradical intermediate.[6] To this end, carbocyclic enediyne frameworks,[7] and more recently, novel metalloenediyne structures,[8–13] have shown considerable promise for the development of molecules with tunable thermal reactivities. Key structural considerations within these architectures are the relative disposition of the alkyne termini, as well as the nature of the ring closing motif, both of which provide steric contributions to the thermal barrier to Bergman cyclization.[14,15] In cases of metal assisted enediyne activation, it is now established that the metal center geometry is an important influence on the cyclization thermodynamics.[11–13] However, the structural consequences derived from ligand design also contribute significantly to the initial barrier height prior to metal assisted activation.[12,13] Unfortunately, the steric influences of the metal binding functionalities have not yet been systematically evaluated for simple enediyne ligands.

As a part of our ongoing investigations of novel metalloenediyne structures and reactivities,[11–13,16] we became interested in designing simple nitrogen donor enediyne chelates with variable thermal properties. Within this theme, we report the syntheses and thermal reactivities of two symmetric and two asymmetric enediyne chelates of the form 1,8-bis(R,R′)oct-4-ene-2,6-diyne where R and R′ = dimethylamino, amino, or 3-hydroxypyridine. The asymmetric compounds are synthetically unique, and exhibit cyclization temperatures between the bis(dimethylamino) and the novel diamino compound, the latter of which is substantially more reactive. The thermal reactivities of these enediynes systematically illustrate the importance of intraligand steric hindrance in influencing Bergman cyclization temperatures.

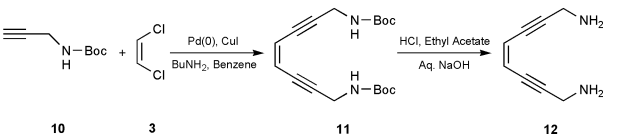
Scheme 1 illustrates the general strategy for our preparation of the symmetric dimethylamino enediyne (1,8-bis(dimethylamino)oct-4-ene-2,6-diyne,[17] **4**),† as well as the dimethylamino (**5**)‡ and 3-hydroxypyridine (**6**) substituted 5-chloropent-4-ene-2-yne synthon. Stephens–Castro coupling of 2.2 equiv. of the 3-dimethylaminoprop-1-yne (**1**) with *cis*-1,2-dichloroethylene (**3**) over a Pd(0) catalyst in the presence of CuI and $BuNH_2$ generates **4** in 79% yield. Comparable reaction conditions using 1 : 1.2 alkyne **1**,**2** : **3** stoichiometries produces the monosubstituted eneyne precursors **5**, **6** in 57–62% yield. Reaction of **5** with 1 equiv. of the *N*-Boc-prop-2-ynyl amine (**10**), or **6** with **1** under analogous conditions yields the asymmetric products **7** and **8**§ (Scheme 2). Subsequent treatment of **7** with acid removes the protecting group and generates the asymmetric primary/tertiary amine species **9**.§ The same *N*-Boc-prop-2-ynyl amine (**10**) is employed for the preparation of the *N*-Boc enediyne precursor **11** and the subsequent diamino product **12** by analogy (Scheme 3).¶



Scheme 1



Scheme 2



Scheme 3

The Bergman cyclization temperatures of enediyes **4**, **8**, **9**, and **12** (Table 1) were measured on neat materials by DSC and show a remarkable 80 °C variation across the series. The origin of the gradient derives from the steric encumbrance imposed upon the alkyne termini by the nitrogen-containing substitutents at the 1,8 positions of the enediyne framework. Beginning with R = dimethylamino, **4** is a thermally stable compound that exhibits a Bergman cyclization temperature of 186 °C. Substitution of one dimethylamino group with 3-hydroxypyridine (**8**) dramatically reduces the Bergman cyclization temperature to 149 °C. The result derives primarily from two sources. First, the ability of the pyridine ring to rotate out of the enediyne plane about the oxygen bond relieves steric clashes with the opposing substituent.[13] Secondly, the addition of the sp^3 oxygen between the pyridine ring and the alkyne termini

Table 1 Bergman cyclization temperatures of symmetric and asymmetric acyclic enediynes

Compound	Cyclization temperature/°C
4	186
8	149
9	139
12	106
13	136[12]
14	195[13]

DOI: 10.1039/b007360l

effectively distances the pyridine substituent from the alkyne termini by another atom, further reducing the interaction between substituents. This latter effect plays an important role as subsequent substitution to form the 1,8-bis(pyridin-3-yloxy)oct-4-ene-2,6-diyne (**13**) compound[12,16] restores the adjacent proximity of the substituents and results in only a modest decrease of the Bergman cyclization temperature of **13** (136 °C) relative to **8**. In contrast, removal of oxygen and methylene carbon atoms from **13** to form the conjugated 1,6-dipyridin-3-ylhex-3-ene-1,5-diyne (**14**) in which the pyridine rings are adjacent to the alkyne termini restores the high Bergman cyclization temperature (195 °C).[13]

A more pronounced trend is observed between the three compounds in the bis(dimethylamino) to diamino enediyne series (**4**, **9**, **12**). Monosubstitution of amino for dimethylamino (**9**) yields a dramatic 47 °C decrease in the Bergman cyclization temperature (**9** = 139 °C). Further substitution to form the diamino compound **12** produces an additional 33 °C decrease in the Bergman cyclization temperature (**12** = 106 °C, onset: 55 °C) indicating that **12** has one of the most facile thermal reactivities of an acyclic enediyne reported to date. The enhanced thermal reactivity of **12** results from a combination of the reduced steric hindrance of the primary amine functionalities, as well as an additional contribution from intramolecular hydrogen bonding.

To better correlate the thermal reactivity of **12** with that of other enediyne compounds reported in solution, we have measured the pseudo first-order rate constant (20-fold cyclohexadiene) and half-life ($t_{1/2}$) for the reactivity of **12** in DMSO by monitoring the disappearance of the –CH– ^{1}H NMR resonance at 5.7 ppm at 65 °C. A first order plot of ln([**12**]) *vs.* *t* and subsequent linear regression (R = 0.99) yielded k_{obs} = 4.16×10^{-2} h^{-1}, $t_{1/2}$ = 16.6 h. As is often observed in solution cyclization reactions of enediynes, a series of products are produced,[18] which in this case include disubstituted benzenes, and as such no dominant species could be isolated from the reaction. The low onset temperature for reactivity of this acyclic enediyne indicates that **12** may be an extremely important ligand for generating thermally reactive and therapeutically useful metalloenediyne complexes. The series also highlights the importance of ligand design in influencing Bergman cyclization temperatures and points toward the use of sterically innocent ligands in order to achieve lower metalloenediyne cyclization temperatures.

The generous support of the American Cancer Society (RPG-99-156-01-C), the Donors of the Petroleum Research Fund (PRF#33340-G4), administered by the American Chemical Society, and Research Corporation (Research Innovation Award #RI0102 for J. M. Z) are gratefully acknowledged.

Notes and references

† Symmetric enediyne (**4**)[17] was prepared by adding alkyne (2.2 mol) in a mixture of *cis*-1,2-dichloroethylene (1 mol), $Pd(PPh_3)_4$ (0.06 mol), CuI (0.2 mol), *n*-butylamine (5 mol) in benzene at 45 °C and stirring the mixture for 4 h at that temperature. The crude product was purified by flash column chromatography (5% ethyl acetate–dichloromethane). Spectral data for (**4**), yield: 79%; δ_H(400 MHz, $CDCl_3$): 2.19 (s, 12H, CH_3), 3.33 (s, 4H, NCH_2), 5.71 (s, 2H, CH); δ_C($CDCl_3$): 44.16 (NCH_3), 48.84 (NCH_2), 83.02 (Cquart), 93.34 (Cquart), 119.38 (CH); MS: *m/z* 191.2 (M^+ + 1).

‡ Spectral data for (**5**), yield: 62%; δ_H(400 MHz, $CDCl_3$): 2.32 (s, 6H, NCH_3), 3.44 (s, 2H, NCH_2), 5.88 (d, J = 8 Hz, 1H, CH), 6.36 (d, J = 8 Hz, 1H, CH); δ_C($CDCl_3$): 44.39 (NCH_3), 48.93 (NCH_2), 79.50 (Cquart), 93.64 (Cquart), 112.24 (CH), 128.25 (CH); MS: *m/z* 145 (M^+ + 2), 143 (M^+). Spectral data for (**6**), yield: 57%; δ_H(400 MHz, $CDCl_3$): 4.95 (s, 2H, OCH_2), 5.90 (d, J = 8 Hz, 1H, CH), 6.46 (d, J = 8 Hz, 1H, CH), 7.25-7.33 (m, 2H), 8.27 (m, 1H), 8.42 (s, 1H); δ_C($CDCl_3$): 56.95 (OCH_2), 82.0 (Cquart), 91.23 (Cquart), 111.28 (CH), 121.94 (CH), 123.98 (CH), 130.97 (CH), 138.70 (CH), 143.05 (CH), 153.94 (Cquart); MS: *m/z* 195 (M^+ + 2), 193 (M^+), 158, 130.

§ Spectral data for (**7**), yield: 65%; δ_H(400 MHz, $CDCl_3$): 1.45 (s, 9H, CH_3), 2.35 (s, 6H, NCH_3), 3.46 (s, 2H, NCH_2), 4.12 (s, 2H, NCH_2), 5.09 (s, 1H, NH), 5.82 (m, 2H, CH); δ_C($CDCl_3$): 28.66 (CH_3), 31.66 (NCH_2), 44.34 (NCH_3), 49.04 (NCH_2), 80.17 (Cquart), 81.03 (Cquart), 82.96 (Cquart), 93.09 (Cquart), 92.18 (Cquart), 119.18 (CH), 120.29 (CH), 155.59 (CO); MS: *m/z* 262.16 (M^+); Spectral data for (**8**), yield: 62%; δ_H(400 MHz, $CDCl_3$): 2.28 (s, 6H, NCH_3), 3.39 (s, 2H, NCH_2), 4.90 (s, 2H, OCH_2), 5.78 (d, J = 8 Hz, 1H, CH), 5.88 (d, J = 8 Hz, 1H, CH), 7.20–7.27 (m, 1H), 7.28–7.31 (m, 1H), 8.25 (m, 1H), 8.38 (d, J = 4 Hz, 1H); δ_C($CDCl_3$): 44.25 (NCH_3), 48.87 (NCH_2), 57.12 (OCH_2), 82.65 (Cquart), 85.51 (Cquart), 90.19 (Cquart), 93.72 (Cquart), 118.14 (CH), 121.36 (CH), 121.89 (CH), 124.02 (CH), 138.66 (CH), 143.04 (CH), 154.13 (Cquart); MS: *m/z* 239.1 (M^+ − 1), 196.1, 145.1. Spectral data for (**9**), yield: 72%; δ_H(400 MHz, $CDCl_3$): 1.42 (br s, 2H, NH_2), 2.34 (s, 6H, NCH_3), 3.47 (s, 2H, NCH_2), 3.67 (s, 2H, NCH_2), 5.81 (s, 2H, CH); δ_C($CDCl_3$): 32.34 (NCH_2), 44.33 (NCH_3), 49.02 (NCH_2), 80.36 (Cquart), 83.04 (Cquart), 92.65 (Cquart), 119.43 (CH), 119.49 (CH); MS: *m/z* 162.1 (M^+), 132.1.

¶ The syntheses of **11** and **12** are directly analogous to that of **4** and **9**. Spectral data for enediyne (**11**), yield: 68%; δ_H(400 MHz, $CDCl_3$): 1.44 (s, 18H, CH_3), 4.10 (s, 4H, NCH_2), 4.93 (br s, 2H, NH), 5.78 (s, 2H, CH); δ_C($CDCl_3$): 28.67 (CH_3), 31.65 (NCH_2), 80.29 (Cquart), 80.55 (Cquart), 93.70 (Cquart), 119.91 (CH), 155.68 (CO); MS: FAB 335 (M^+ + 1). Deprotection of the Boc group was achieved by stirring (**11**) with 37% HCl in ethyl acetate. Spectral data for (**12**), yield: 70%; δ_H(400 MHz, $CDCl_3$): 1.44 (s, 4H, NH_2), 3.54 (s, 4H, NCH_2), 5.72 (s, 2H, CH); δ_C($CDCl_3$): 32.52 (NCH_2), 79.90 (Cquart), 98.21 (Cquart), 119.15 (CH); MS: *m/z* 134.1 (M^+ + 1).

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